Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WO 27815		
International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/EP00/07315	28 July 2000 (28.07.00)	13 August 1999 (13.08.99)

International Patent Classification (IPC) or national classification and IPC
A61K35/00

Applicant
WIELAND, Heinrich

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17 January 2001 (17.01.01)	06 December 2001 (06.12.2001)
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP00/07315

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-39 . as originally filed
pages _____ . filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:

pages 1-26 , as originally filed
pages _____ , as amended (together with any statement under Article 19
pages _____ . filed with the demand
pages _____ , filed with the letter of _____

☒ the drawings:

pages 1/2-2/2 . as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:

pages _____ . as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

See the supplemental box

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP00/07315

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-19, 23 concerning IA, 1-26 in part concerning N, IS, IA

because:

☒ the said international application, or the said claims Nos. 1-19,23
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See the supplemental box

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1-26 (in part) .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

See the supplemental box

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. _____

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: II

The claimed priority is only partially valid since the following features are not set out in the priority document:

- inhibition of the formation and/or the effect of dihydrotestosterone (Claim 8),
- combination of an aromatase inhibitor with a 5-alpha-reductase inhibitor (Claims 9, 10, 24-26),
- prevention of cardiac or cerebral infarction (Claim 15),
- prevention or treatment of osteoporosis (Claim 16)
- prevention or treatment of atherosclerosis (Claim 17)
- prevention or treatment of urinary incontinence (Claim 18)
- prevention or treatment for excessive glucocorticoid formation (Claim 19)
- reduction of hair growth in women (Claim 20)
- reduction of exposure to sun on the skin (Claim 22).

The priority of the claims referring to the claims mentioned is therefore only partially or not valid. The same remark applies at least partially to the claims that contain the subjects mentioned.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

As established by the international searching authority, valid Claims 1 to 26 refer to a product/ a compound/ a therapeutic use, each characterised by a desired pharmacological profile, i.e. the activity as an inhibitor of the effect of oestrogens, as aromatase inhibitors and 5-alpha-reductase inhibitors, for restoring collagen. The claims therefore involve all products, diseases, etc. that have this property or quality, whereas the application is supported by the description in the sense of PCT Article 5 only for a limited number of these products etc. In the present case the claims lack the corresponding support and the application does not contain the disclosure required to such a level that it does not seem possible to carry out a useful search over the entire desired protective scope. Despite that, the claims also lack the clarity stipulated in PCT Article 6 since there is an attempt therein to define the use by the result desired in each case. This lack of clarity is such that it makes it impossible to carry out a useful search for the first invention over the entire protective scope desired. Consequently, the search related to the parts of the claims which, in the aforementioned sense, seems to be clearly supported or disclosed, i.e. those parts concerning the products that are established in Claim 4 and in Examples 1 and 5.

Pursuant to PCT Rule 66.1(e), the preliminary examination is restricted to the searched subjects, i.e. **Claims 1 to 26 (in part)**.

Claims 1 to 19, 23 refer to subject matter that is

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

covered by PCT Rule 67.1(iv) in the opinion of this Examining Authority. Consequently, no report has been established about the industrial applicability of the subject matter of these claims (PCT Article 34(4)(a)(i)).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV

An objection about the lack of unity of invention was raised during the international search with respect to the present application.

The different inventions/groups of inventions investigated during the international search are:

1. Claims 1 to 14, 23 (in part), 15, 17

Use of aromatase inhibitors for treating cardiac and cerebral infarction and atherosclerosis.

2. Claims 1 to 14, 23 (in part), 16

Use of aromatase inhibitors for treating osteoporosis.

3. Claims 1 to 14, 23 (in part), 18

Use of aromatase inhibitors for treating urinary incontinence.

4. Claims 1 to 14, 23 (in part), 19

Use of aromatase inhibitors for treating excessive glucocorticoid formation.

5. Claims 1 to 14, 23 to 26 (in part), 20 to 22

Use of aromatase inhibitors for cosmetic treatment of hair and skin.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV

6. Claims 1 to 14, 23 (in part), 15, 17

Use of anti-oestrogens for treating cardiac and cerebral infarction and atherosclerosis.

7. Claims 1 to 14, 23 (in part), 16

Use of anti-oestrogens for treating osteoporosis.

8. Claims 1 to 14, 23 (in part), 18

Use of anti-oestrogens for treating urinary incontinence.

9. Claims 1 to 14, 23 (in part), 19

Use of anti-oestrogens for treating excessive glucocorticoid formation.

10. Claims 1 to 14, 20 to 23 (in part), 24 to 26

Use of anti-oestrogens for cosmetic treatment of hair and skin.

The problem to be solved by the present invention can therefore be considered to be that of influencing extragonadal sex hormone formation in a favourable manner to produce therapeutic effects.
The solutions proposed for this problem in the present application are the use of anti-oestrogen compounds and

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV

aromatase inhibitors that have the capacity to influence collagen-containing body parts.
The use of anti-oestrogen compounds and aromatase inhibitors is claimed for treating:

1) infarction and atherosclerosis
2) osteoporosis
3) urinary incontinence
4) excessive glucocorticoid formation
5) cosmetic problems of skin and hair.

A pharmaceutical use of anti-oestrogen compounds is already known.
For example,
EP 0776661: Use of anti-oestrogen compounds to treat collagen diseases.
The use of anti-oestrogen compounds to influence collagen-containing body parts is already disclosed and cannot therefore act as a single general inventive concept as defined in PCT Rule 13 that represents the technical relationship between the claimed inventions.
The use of aromatase inhibitors to treat some of these diseases is already known.
For example,
WO 96 08231: Use of aromatase inhibitors to reduce hair growth.
DE 3338212: Use of aromatase inhibitors to treat infarction. The concept of using aromatase inhibitors and anti-oestrogens to treat these diseases is already disclosed and cannot therefore act as a single general inventive concept as defined in PCT Rule 13 that

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV

represents the technical relationship between the claimed inventions.

The claimed inventions are simply alternative solutions that are each characterised by their own special technical features. There is no other technical feature in the present application that determines a technical relationship among the inventions in the form of a "particular technical feature". The requirement for unity of invention pursuant to PCT Rule 13 is therefore not satisfied.
The individual inventions are identified as the different aforementioned subjects.

The applicant was not requested to delimit the application or to pay additional examination fees.

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	18, 19 (in part)	YES
	Claims	1-17, 20-26 (in part)	NO
Inventive step (IS)	Claims		YES
	Claims	1-26 (in part)	NO
Industrial applicability (IA)	Claims	20-22, 24-26 (in part)	YES
	Claims		NO

2. Citations and explanations

Due to the objections raised in Box III with respect to clarity of the present application, this statement with regard to novelty, inventive step and industrial applicability is only established for **Claims 1 to 26 (in part)**.

1. This report makes reference to the following documents; where it is not otherwise indicated, the international search report citations are considered relevant.

D1 DATABASE CHEMAB [Online] CHEMICAL ABSTRACTS SERVICE COLUMBUS, OHIO, US; MORITA, KYOKO ET AL: "Effect of soybean isoflavone on bone metabolism" retrieved from STN Database accession no. 133:16833 XP002161790 & DAIZU TANPAKUSHITSU KENKYU (1999), 2,76-82,

D2 EP-A-0 776 661 (ORION YHTYMAE OY; NIPPON KAYAKU KK (JP)) 4 June 1997 (1997-06-04)

D3 DE-A-33 38 212 (SCHERING AG) 25 April 1985 (1985-04-25)

D4 WO-A-96 08231 (UNIV SHEFFIELD; MESSENGER ANDREW GUY (GB)) 21 March 1996 (1996-03-21)

D5 WO-A-97 36570 (S W PATENTVERWERTUNGS GES M B;

SCHMIDT ALFRED (DE); WIELAND HEINRI) 9 October 1997 (1997-10-09) additional relevant passages: Example 3

D6 WO-A-91 00731 (ENDORECHERCHE INC) 24 January 1991 (1991-01-24)

D7 WO-A-92 18132 (MERCK & CO INC) 29 October 1992 (1992-10-29)

D8 US-A-5 906 987 (CHWALISZ KRISTOF ET AL) 25 May 1999 (1999-05-25)

D9 US-A-5 280 035 (BOHLMANN ROLF ET AL) 18 January 1994 (1994-01-18) further relevant passages: column 3, lines 36 to 52, column 6, lines 7 to 19

D10 EP-A-0 684 235 (MOCHIDA PHARM CO LTD) 29 November 1995 (1995-11-29)

D11 US-A-5 494 899 (KINCADE PAUL W ET AL) 27 February 1996 (1996-02-27)

D12 THESEN: "formestane, a new aromatase inhibitor" PHARM. ZTG., vol. 141, no. 26, 1996, pages 32 to 40, XP000986872.

2. Novelty (PCT Article 33(2))

The following points should be taken into consideration for the assessment of novelty:
The applicant has shown that particular diseases like osteoporosis, cardiac infarction, cerebral infarction and atherosclerosis can be treated by oestrogen inhibitors by way of the mechanism of stabilising, increasing or restoring of collagen. However, the knowledge of the involved mechanism would only improve understanding of the associated treatment, and a person skilled in the art would not change his/her treatment. Identifying the mechanism can therefore not re-establish the novelty of the

treatment methods.

Disclosing the treatment of the diseases mentioned by representing the functionally defined substance class is therefore prejudicial to novelty for independent Claim 1.

The following claims are anticipated by the prior art and are therefore not novel, as defined in PCT Article 33(2):

Claims 1 to 3, 13, 14 by the documents D3, D4, D5, D8, D9 and D11.

Claims 4, 5, 7 by D5, **Claim 6** by D5, D9, **Claim 11** by D3, D4, D5, D9, **Claim 12** by D4, D5, D9, **Claims 8, 9 and 10** by D5, D8, **Claim 15** by D3 and D9, **Claim 16** by D6, D11, **Claim 17** by D8, **Claim 20** by D12, **Claims 21, 22** by D5, **Claim 23** by D3, D5, D8, D9, D11, **Claims 24 to 26** by D5, D7.

The technical features of **Claims 18, 19 (in part)** are not described in the cited prior art and therefore seem to be novel, as defined in PCT Article 33(2).

3. Inventive step (PCT Article 33(3))

The technical effect of **Claims 18 and 19** was not substantiated but simply involves purely theoretical observations. These claims cannot therefore be said to involve inventive step.

Moreover, **Claim 19** is not inventive in relation to D10.

4. Industrial applicability (PCT Article 33(4))

The PCT Contracting States do not have uniform

criteria for assessing the industrial applicability of **Claims 1 to 19, 23 to 26 (in part) in their present form**. Patentability may depend on the wording of the claims. The EPO, for example, does not recognise the industrial applicability of claims to the medical use of a compound; it does, however, allow claims to the first medical use of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: VI

Application no. Patent no.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (day/month/year)
WO9962480	09/12/1999	28/05/1999	29/05/1998
WO9962459	09/12/1999	03/06/1999	05/06/1998
US5972921	26/10/1999	12/12/1997	